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Review

Mechanistic aspects of the interaction between selenium and arsenic ☆

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Abstract

Selenium is an essential trace element for humans and other animals, and there is mounting evidence for the efficacy of certain forms of selenium as cancer-chemopreventive compounds. However, over the years, numerous elements such as As, Cu, Zn, Cd, Hg, Sn, Pb, Ni, Co, Sb, Bi, Ag, Au, and Mo have been found to inhibit anti-carcinogenic effects of selenium, which may affect the anti-carcinogenic activity of selenium. The interaction between selenium and arsenic has been one of the most extensively studied. The proposed mechanisms of this interaction include the increase of biliary excretion and direct interaction/precipitation of selenium and arsenic, and their effects on zinc finger protein function, cellular signaling and methylation pathways. This article focuses on these proposed mechanisms and how anti-carcinogenic effects of selenium may be affected by arsenic.
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1. Introduction

Selenium (Se) is an essential trace element for humans and animals, and is required for the growth of mammalian cells in culture [1,2]. The current recommended dietary daily allowance for Se is 55 μg for healthy adults [3]. At such intakes, Se supports the expression of a variety of selenoproteins through the tRNA-mediated incorporation of selenocysteine. These selenoproteins include glutathione peroxidases and thioredoxin reductases, which have important antioxidant and detoxification functions. In addition, a cancer-chemoprotective effect of Se has been observed [4–7].

Interest in the study of Se status and cancer risk has been stimulated by the landmark finding that supplementation of a moderate daily dose of Se could substantially reduce cancer risk in humans [8]. Some epidemiological studies [9,10] have found that Se status can be negatively associated with cancer risk, and intervention studies [4,8] have found that supplements/high Se intakes are effective in reducing mammary, prostate, lung, colon, and liver cancer risk [4,8]. In experimental animals, anti-carcinogenic effects have been consistently associated with Se at supranutritional intakes (>1 mg/kg diet) that are at least 10 times those required to prevent clinical signs of Se deficiency and to support near-maximal tissue activities of selenoenzymes [7,11].

A number of mechanisms have been proposed that may account for the chemoprotective effects of Se including antioxidant protection, altered carcinogen metabolism, enhanced immune surveillance, cell cycle effects, enhanced apoptosis and inhibition of angiogenesis

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[5,11]. However, the protective functions of Se may be subject to inhibition by numerous elements that may exist in foods or be encountered in the environment, including arsenic (As) [12,13].

There is some evidence suggesting that As can be beneficial for animal growth [14], and pharmacological amounts of As have been shown to be effective treating certain forms of leukemia [15]. However, As is better known for its negative impact on human health. Through epidemiological studies, As exposure has been associated with increased risks to cancers of the lung, skin, bladder, and liver. The US Environmental Protection Agency has classified As as a known human carcinogen (category A) [16,17]. Arsenic exposure is mainly through diet and drinking water. Arsenic is present in the environment in various chemical forms but inorganic As as trivalent arsenite (As^{3+}) and pentavalent arsenate (As^{5+}) are the major forms of As in surface and underground water [17,18].

Although As and Se are metalloids with similar chemical properties, they have dramatically different biological effects. Therefore, biological interactions between As and Se depend upon their respective chemical forms. Antagonistic effects or mutual detoxification between As and Se have been confirmed in many animal species including humans [12,19,20], since 1938 when Moxon discovered that As treatment could protect against Se toxicity in cattle [21]. It is generally accepted that uptake of one of these elements causes release, redistribution, or elimination of the other element by urinary, biliary, and/or expiratory routes [13]. However, the precise mechanism at the cellular level is still unknown. There are several proposed mechanisms to explain the interaction between Se and As, and these mechanistic aspects may shed light on how As may affect the anti-carcinogenicity of Se.

2. Metabolic interaction between arsenic and selenium

Studies of the interaction between As and Se began with the finding that chronic and acute Se toxicities could be minimized by the administration of arsenite and certain other arsenicals [20–23]. Earlier work demonstrated that As markedly increased the excretion of Se into the gastrointestinal tract when both arsenite and selenite were injected at subacute doses [20,24]. In addition, there were roughly corresponding decreases in the amounts of Se retained in the liver. The ability of As to promote the elimination of Se into the gut was observed in many experiments that used different doses, forms of As and Se, and time intervals between the As and Se injections [24]. Also, As decreased the amount of Se in the carcass, blood, and expired air, but the administration of large doses of an organic arsenical, sodium arsanilate, decreased the elimination of Se into the gastrointestinal contents and increased the amounts in the expired air, and the net effect being a slight decrease in Se retained in the carcass [24]. Conversely, it was found that selenite stimulated the gastrointestinal excretion of As in experiments similar to those in which As stimulated the gastrointestinal excretion of Se [24]. Further study demonstrated that As greatly increased the amount of Se excreted in rat bile [24,25]. This key observation was seen with several forms of Se and As over a wide dose range, and the large amounts of Se excreted in the bile of rats treated with As were approximately equivalent to the decreases in the retention of Se in the liver [25]. Therefore, it was proposed that Se and As reacted in the liver to form a conjugate that was excreted into bile; such an explanation is consistent with the fact that As and Se each increase the biliary excretion of the other [20,25].

More recently, it has been demonstrated that the in vivo antagonism between arsenite and selenite has its molecular basis in the formation of a novel As–Se compound: seleno-bis (*S*-glutathionyl) arsinium ion, $[(GS)_2AsSe]^-$, which is subsequently excreted in bile [26]. The detection of $[(GS)_2AsSe]^-$ in bile after intravenous injection of rabbits with selenate and arsenite suggests that both metalloids are first translocated to the liver [26]. The current hypothesis is that selenate is first reduced to selenite and, then, to selenide by a putative selenate reductase and/or reduced glutathione (GSH) [26]. Because of high intracellular concentrations of GSH in hepatocytes, the OH groups of arsenite are thought to be substituted by glutathionyl moieties forming the known compound $(GS)_2As–OH$ [26]. Selenide may then react with $(GS)_2As–OH$ to form $[(GS)_2AsSe]^-$. The latter could then be exported from the hepatocytes to bile by ATP-driven glutathione *S*-conjugate export pumps [27]. This observation provides the chemical basis that As and Se each increase the biliary excretion of the other at high/toxic dose ranges [20,25]. However, the existence of an interaction between As and Se through the biliary excretion at normal Se and As daily intakes (low dose ranges) still remains to be determined.

3. Direct arsenic and selenium interaction/precipitation

Although increased biliary excretion of Se may be the principal mechanism by which As interacts with Se, other mechanisms may also be important. The direct interaction of minerals in aqueous solutions may also play a major role in dissolution, precipitation, and absorption processes [28,29]. Many chemical forms of As and Se have been observed in nature but the relative quantitative importance of the forms vary very much. In the environment and diets, Se occurs in the +6 oxidation state as selenate (contain SeO_4^{2-}), +4 oxidation state as selenite (contain SeO_4^{2-}), 0 oxidation state as elemental

Se, −1 oxidation state as selenocystine, and −2 oxidation state as selenocysteine. Similarly, As can occur in the +5 oxidation state as arsenate (contain AsO_4^{2-}), +3 oxidation state as arsenite (contain AsO_3^{3-}), 0 oxidation state as elemental As, and the −1 and −2 oxidation states as in arsenical pyrites. In general, reduced inorganic As found in sulfide minerals has relatively low toxicity; whereas oxidized inorganic As^{3+} and As^{5+} compounds are significantly more toxic [28].

Because of their similar physical and chemical properties (i.e., similar valence shells, electronic structures, and atomic radii), As and Se compounds can be biologically antagonistic to each other [30,31]. For example, both Se^{4+} and As^{3+} have the same electronic structure (their 4p and 4d orbitals are without electrons). This similarity of electronic structure results in selenite (Se^{4+}) absorption being markedly depressed by arsenite (As^{3+}) on tissue or organelle membrane as shown in a chick model [30,31].

Berry and Galle [32] used electron microanalysis in conjunction with a transmission electron microscope to study the interaction of Se and As in renal cells [32]. In cells from the proximal convoluted tubule, microanalysis showed the presence of both Se and As in dense deposits in the intracytoplasmic lysosomes and in dense deposits eliminated in the urinary lumen. Furthermore, the deposits contained a constant ratio of Se and As and was in the form of insoluble selenide (As_2Se). These deposits, which were concentrated in lysosomes, were not detected in the cytoplasm [32]. Subsequently, these lysosomes and their precipitate are eliminated in the urine in vivo [32]. These findings provide direct evidence of the interaction between Se and As at the sub-cellular level, which directly contribute to the observed mutual detoxification between As and Se at metabolic level.

4. The effect of selenium and arsenic on zinc finger protein function

Chemically, Se qualitatively resembles sulfur, but has much greater oxidoreductive potential particularly when combined with zinc. Zinc finger structures are among the most abundant protein motifs in the eukaryotic genome and have diverse biological functions in many cellular processes [33]. They are present not only in transcription factors, but in all families of proteins involved in maintaining genomic stability, including DNA repair proteins and cell cycle control proteins [33]. It has been estimated that about 3% of the identified genes encode proteins with zinc finger domains [34]. Selenium can substitute for the sulfur of cysteine, yet differs from it in redox potential and stability of its oxidation states. The catalytic role of selenocysteine in glutathione peroxidase is based upon this redox trait; i.e., the Se atom changes its oxidation states in the course of the catalytic cycle [35,36]. A remarkable feature of Se is its ability to oxidize thiols under reducing conditions such as those found in the cytosol [10,35–37]. For example, low concentrations of Se compounds of reducible oxidation states such as selenocystamine (diselenide) can release zinc ions from metallothionein through the oxidation of thiol groups [38]. The released zinc may then be available for the apoforms of zinc enzymes that have inherently lower stability constants [36,38]. Interestingly, the complexation of zinc in metallothionein is similar to the tetrahedral zinc ion complexation present in one of the major classes of transcription factors and other zinc-finger proteins. This suggests that reducible Se compounds can target zinc–sulfur bonds, not only in metallothionein but in zinc fingers, zinc twists, and in many transcription factors and signaling proteins [36,38,39]. Consistent with the above observation, recent studies demonstrated that low concentrations of Se compounds in reducible oxidation states may interfere with DNA repair processes by inactivation of DNA repair proteins [39,40]. For example, the reducible Se compounds phenylseleninic acid, phenylselenyl chloride, selenocystine, ebselen, and 2-nitrophenylselenocyanate caused a concentration-dependent decrease in activity of Fpg, a zinc-finger protein involved in DNA repair, while no inhibition was detected with fully reduced selenomethionine, methylselenocysteine or some sulfur-containing analogs [39,40]. The reducible Se compounds also inhibited zinc finger protein–DNA binding and released zinc from the zinc finger motif [39–41]. Because redox reactions are important for the regulation of zinc finger proteins and thus the cellular pathways that are dependent on these proteins, an imbalance in Se compounds, as powerful mediators of cellular redox reactions, provoked by either Se deficiency or oversupply, may considerably decrease genomic stability [39]. Similarly, zinc finger proteins are sensitive intracellular targets for arsenite. For example, starting at low micromolar concentrations, all trivalent arsenic compounds provoked zinc release from the zinc finger domain of the xeroderma pigmentosum group A protein (XPA); monomethylarsonous (MMA(III)) and dimethylarsinous (DMA(III)) were found to be more reactive than arsenite [40]. Based on these findings, it is conceivable that Se and As may not always antagonize each other but may have additive or even synergistic detrimental effects because zinc finger proteins are involved in virtually all cellular reactions required to maintain genomic stability; their inactivation may lead to increased genetic instability.

5. The effect of selenium and arsenic on cellular signaling

The effects of Se and As on cellular signal transduction have been actively studied in the past few years

[19,42]. Arsenic activates several signaling pathways including the mitogen-activated protein kinase (MAPK) and the NFκB signaling and DNA repair pathways related to the generation of reactive oxygen species. The activation protein 1 (AP-1) and nuclear factor-κB (NFκB) are representative members of two distinct families of heterodimeric transcriptional complexes that have been implicated in stimuli-induced changes in gene expression [43]. Several lines of evidence have demonstrated that As^{3+} and As^{5+} enhance AP-1 and NFκB DNA binding and induce stress protein expression [19,43,44]. As^{3+} and As^{5+} cycle through oxidation and reduction in vivo, and As^{3+} has been generally accepted to be the most harmful metabolite responsible for toxic and carcinogenic effects. However, recent studies have shown that the methylated trivalent arsenicals, methylarsonous acid (MAs^{3+}), and dimethylarsenious acid ($DMAs^{3+}$) are more potent than As^{3+} in the activation of AP-1, cytotoxins and genotoxins [45]. C-Jun N-terminal kinase (JNK) is a member of the stress-activated protein kinase family and is activated by cellular stress. It has been reported that As activates AP-1 activity by inhibiting a JNK protein tyrosine phosphatase and that the activation of JNK/AP-1 results from a defect in turning off the activated JNK. Thus, both As^{3+} and As^{5+} induce apoptosis through the JNK pathway [46,47]. In contrast, numerous studies indicate that through redox regulation, Se-containing compounds attenuate oxidation related JNK AP-1 and NFκB activation [19,48,49]. Apoptosis caused by As is dependent on activation of AP-1, whereas that by selenite is not [19]. Our work has demonstrated that at the molecular level, the antagonism between Se and As occurs because Se^{4+} inhibits As^{3+} and As^{5+}-induced JNK/AP1 signaling; the actions of As^{3+}/As^{5+} and Se^{4+} are mediated through their redox effects on important cysteine residues in the JNK phosphatase and JNK/AP-1, respectively [19,48]. At the cellular level, the antagonistic effect between As and Se on the induction of cell apoptosis and necrosis was examined in human leukemia HL-60 cells by co-incubating Na_2SeO_3 with $NaAsO_2/Na_2HAsO_4$ [19]. The occurrence of mineral-induced HL-60 cell apoptosis was Se^{4+} (3 μM) > As^{3+} (50 μM) > As^{5+} (500 μM); concentrations that were higher than those causing apoptosis caused cell necrosis. In addition, the toxic necrotic effect caused by high concentrations of Se^{4+} was neutralized or suppressed by As^{3+}/As^{5+} [19]. Similar to the inhibitory effect of inorganic Se salt compounds (Se^{4+}/Se^{6+}) on As-induced NFκB/AP-1-DNA binding [19], organic Se compounds such as 1,4-phenylenebis(methylene)selenocyanate (p-XSC), ebselen, selenomethionine and selenocysteine also inhibit the DNA-binding activities of the transcription factors NFκB, AP-1 [41,48,49]. In conclusion, Se is likely to inhibit As-activated transcription factor NFκB, AP-1. Similarly, As can suppress Se-toxic necrotic effect. These observations are important additions to the bioactivity profile of Se compounds and would suggest that Se may function as an endogenous ''stop signal'' for As-induced carcinogenic cell signaling.

6. Methylation of arsenic and selenium and the effect of arsenic and selenium on methylation

Formation of methylated metabolites is a critical step in the metabolism of both inorganic Se and As. Inorganic forms of selenite (Se^{4+}) or selenate (Se^{6+}) are reduced by glutathione to yield selenodiglutathione (GS-Se-SG) which is converted to hydrogen selenide (H_2Se) in a reaction catalyzed by glutathione reductase. Hydrogen selenide is thought to be an intermediary metabolite which serves as a precursor for the synthesis of selenocysteine or is methylated to methylselenol, CH_3SeH; dimethylselenide, $(CH_3)_2Se$; and the trimethylselenonium cation, $(CH_3)_3Se^+$. $(CH_3)_3Se^+$ is a major urinary product of Se metabolism and $(CH_3)_2Se$ is a volatile metabolite that is excreted in breath when the capacity for synthesis of $(CH_3)_3Se^+$ has been exceeded [50,51]. Similarly, As^{5+} undergoes reduction to As^{3+} by arsenate reductase (which requires GSH) with subsequent methylation by As methyltransferase to generate methylarsonic acid (As^{5+}). Subsequent reduction and methylation result in di-, and trimethylated metabolites [52,53]. It is assumed that the methylation pathway is directly related to detoxification of As [54,55]. Thus, the reductive metabolism and methylation of both As and Se are linked and complete for the availability of GSH and the methyl donor *S*-adenosylmethionine (SAM). Recently, it has been reported that a concurrent exposure to sodium selenite inhibits methylation of arsenite by recombinant As^{3+}-methyltrasferase in cultured rat hepatocytes [56]. Further studies demonstrated that among sodium selenite, CH_3SeH, $(CH_3)_2Se$, and $(CH_3)_3Se^+$, sodium selenite was the most potent inhibitor of the methylation of arsenite by the As^{3+}-methyltransferase enzyme ($K_i = 1.4$ μM) in cultured cells [57]. The inhibition of As^{3+}-methyltransferase by selenite in cultured hepatocytes appears to be competitive and reversible and may involve direct interaction between selenite and the catalytically active cysteine residues of the enzyme [56]. Overall, these findings demonstrate that inorganic Se and As, at high dose range, mutually inhibit the formation of their methylated metabolites by competing for the limited GSH/SAM and depressing related enzymes.

There is also a proposed nonenzymatic pathway for the methylation of inorganic arsenite [55]. It has been reported that methylvitamin B_{12} (CH_3B_{12}) in the presence of thiols and inorganic arsenite can produce, in vitro, substantial amounts of monomethylarsonic acid (MMA) and small amounts of dimethylarsinic acid

(DMA) in the absence of enzymes [55]. Interestingly, this nonenzymatic methylation of inorganic arsenite by CH_3B_{12} was increased substantially by the presence of dimercaptopropanesulfonate (DMPS) and/or sodium selenite [55]. Therefore, Se may decrease the toxicity of arsenite by activating its nonenzymatic methylation. On the other hand, As is known to interfere with the formation of dimethylselenide from selenite, probably by trapping the intermediary metabolite H_2Se as well as by inhibiting the microsomal enzyme that methylates H_2Se [58]. It is thought that partially methylated forms of Se are more toxic than the fully methylated $(CH_3)_3Se^+$ [59], and the enhancement of the anticarcinogenic activity of $(CH_3)_3Se^+$ by arsenite may be the result of arsenite-mediated inhibition of methyltransferase activity. This would prevent remethylation of the demethylated $(CH_3)_3Se^+$ and thus increase CH_3SeH and $(CH_3)_2Se$ concentrations [60]. Hence, the chemical form of Se determines its interaction with arsenite. With selenite, arsenite decreases CH_3SeH and $(CH_3)_2Se$ concentration, toxicity, and anticarcinogenic activity. However, with $(CH_3)_3Se^+$, arsenite increases CH_3SeH and $(CH_3)_2Se$ concentration, toxicity and anticarcinogenic activity [60]. Thus, the effects of As on methylated Se-metabolites depend on the chemical form of Se. Similarly, sodium selenite also inhibits As-nonenzymatic methylation.

The other important aspect is that Se and As also affect DNA methylation. DNA methylation is an important epigenetic mechanism exerting control of gene expression. Furthermore, epigenetic events are thought to be important in mediating the effects of diet in modifying cancer risk and tumor behavior [61]. The postsynthetic methylation of the 5 position of deoxycytosine residues results in formation of 5-methylcytosine residues in DNA [62]. The reaction is catalyzed by a family of SAM-dependent DNA methyltransferases [62]. Therefore, DNA methyltransferases, as well as Se and As, compete for methyl donation from SAM. It has been shown that As-induced aberrant gene expression may be the result of As-induced DNA hypomethylation in liver epithelial cells [42]. Chronic As exposure results in a dose-dependent depletion of the intracellular SAM pool and global DNA hypomethylation [42]. In contrast, dietary Se deficiency results in global DNA hypomethylation and an increase in colon cancer susceptibility; Se supplementation increased DNA methyltransferase activity and DNA methylation [63]. Therefore, As is likely to antagonize the in vivo Se effect on DNA methylation.

In summary, the interaction between Se and As can occur directly and indirectly depending on the chemical form and dose of each. Although increased biliary excretion of Se may be the principal mechanism by which As interacts with Se, the inorganic salt forms of Se and As can antagonize each other by forming an insoluble precipitate and by mutual inhibition of the formation of methylated metabolites. In addition, Se may function as an endogenous "stop signal" for As-induced carcinogenic cell signaling such as the activation of AP-1 and NFκB. However, the interaction between Se and As may also have synergistic toxic effects by increasing zinc release from critical zinc finger proteins or altering As/Se related metabolic methylation (Fig. 1).

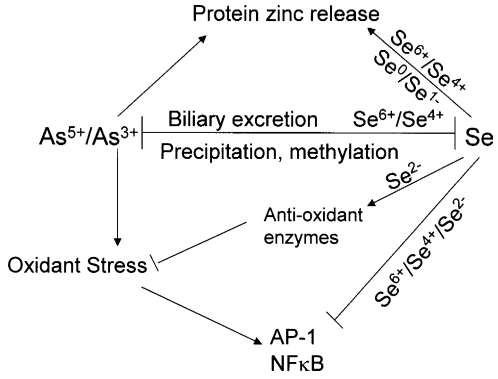

Fig. 1. The effect of the interaction between selenium (Se) and arsenic (As) on cellular metabolic pathways. Arrows represent induction, and single capped lines represent inhibition of pathways; the double capped line represents the mutual inhibition of Se/As bioactivity through the increase of As/Se biliary excretion, the formation of Se–As precipitate, and the modification As/Se methylation pathways.

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